

**WHAT IS CLAIMED IS:**

1. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:
  - a.) an isolated polynucleotide encoding a cell signaling polypeptide involved in the intracellular signaling cascade, or a functional fragment thereof, said polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:7;
  - b.) an isolated polynucleotide comprising the sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:8;
  - c.) an isolated and purified polynucleotide, or fragment thereof, encoding an amino acid sequence of a cell signaling polypeptide involved in the cell signaling cascade, said polypeptide having at least 80% sequence identity with the sequence of SEQ ID NO:2 or SEQ ID NO:4;
  - d.) an isolated polynucleotide comprising a nucleic acid sequence having (i) a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:8; (ii) a nucleic acid sequence degenerate from the sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:8 as a result of genetic code redundancy, or (iii) a complementary nucleic acid sequence thereto;
  - e.) an isolated polynucleotide encoding a human RET16 polypeptide;
  - f.) an isolated polynucleotide comprising nucleotides 151 to 1575 of SEQ ID NO:1, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 476 of SEQ ID NO:2 minus the start codon;
  - g.) an isolated polynucleotide comprising nucleotides 148 to 1575 of SEQ ID NO:1, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 476 of SEQ ID NO:2 including the start codon;
  - h.) an isolated polynucleotide having a nucleotide sequence at least 82.0% identical to SEQ ID NO:12

- i.) an isolated polynucleotide encoding a human RET16.2 polypeptide;
- j.) an isolated polynucleotide comprising nucleotides 114 to 1262 of SEQ ID NO:12, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 384 of SEQ ID NO:13 minus the start codon;
- k.) an isolated polynucleotide comprising nucleotides 111 to 1262 of SEQ ID NO:12, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 384 of SEQ ID NO:13 including the start codon;
- l.) an isolated polynucleotide encoding a human RET16.3 polypeptide;
- m.) an isolated polynucleotide comprising nucleotides 139 to 1641 of SEQ ID NO:14, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 502 of SEQ ID NO:15 minus the start codon;
- n.) an isolated polynucleotide comprising nucleotides 136 to 1641 of SEQ ID NO:14, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 502 of SEQ ID NO:15 including the start codon;
- o.) an isolated polynucleotide encoding a mouse RET16 polypeptide;
- p.) an isolated polynucleotide comprising nucleotides 22 to 1443 of SEQ ID NO:6, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 475 of SEQ ID NO:4 minus the start codon;
- q.) an isolated polynucleotide comprising nucleotides 19 to 1443 of SEQ ID NO:6, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 475 of SEQ ID NO:7 including the start codon;
- r.) the polynucleotide according to any one of (a) through (q), having the nucleic acid sequence of ATCC Accession No. PTA-3161;
- s.) a polynucleotide which is fully complementary to the polynucleotide according to any one of (a) through (r),
- t.) an isolated polynucleotide wherein the complementary nucleic acid sequence hybridizes to either strand of a denatured, double-stranded

polynucleotide comprising the nucleic acid sequence selected from any one of (a) through (r) under conditions of moderate or high stringency;

- u.) the polynucleotide according to (t), wherein the conditions of moderate stringency comprise washing in 0.2x SSPE or SSC and 0.2% SDS at a temperature of about 42°C to about 50°C;
- v.) the polynucleotide according to (t), wherein the conditions of high stringency permit hybridization of those nucleic acid sequences that form stable hybrids in 0.018 M NaCl at about 65°C;
- w.) an isolated and purified polynucleotide, or fragment thereof, encoding an amino acid sequence of a cell signaling polypeptide involved in the cell signaling cascade, said polypeptide having at least 82% sequence identity with the sequence of SEQ ID NO:13;
- x.) an isolated and purified polynucleotide, or fragment thereof, encoding an amino acid sequence of a cell signaling polypeptide involved in the cell signaling cascade, said polypeptide having at least 95% sequence identity with the sequence of SEQ ID NO:15;
- y.) an isolated and purified polynucleotide, or fragment thereof, having at least 68.2% sequence identity with the sequence of SEQ ID NO:12; and
- z.) an isolated and purified polynucleotide, or fragment thereof, having at least 93.1% sequence identity with the sequence of SEQ ID NO:14.

2. A composition comprising the polynucleotide according to claim 1.

3. An expression vector containing the polynucleotide according to claim 1.

4. A host cell containing the expression vector according to claim 3.

5. A substantially purified cell signaling protein comprising a polypeptide sequence selected from the group consisting of:

- a.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:2 or SEQ ID NO:4;

- b.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 90% sequence identity to the sequence set forth in SEQ ID NO:2 or SEQ ID NO:4;
- c.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO:2 or SEQ ID NO:4;
- d.) an isolated and substantially purified human cell-signaling protein involved in the cell signaling cascade and encoded by the nucleic acid sequence of ATCC Accession No. PTA-3161;
- e.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 80% sequence identity to the sequence set forth in SEQ ID NO:7 or SEQ ID NO:9;
- f.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 90% sequence identity to the sequence set forth in SEQ ID NO:7 or SEQ ID NO:9;
- g.) a substantially purified cell signaling protein involved in the cell signaling cascade and encoded by a polynucleotide having a nucleic acid sequence as set forth in SEQ ID NO:1 or SEQ ID NO:3, or a nucleic acid sequence degenerate from that of SEQ ID NO:1 or SEQ ID NO:3 as a result of redundancy of the genetic code;
- h.) a substantially purified cell signaling protein having the amino acid sequence as set forth in SEQ ID NO:7 or SEQ ID NO:9;
- i.) an isolated polypeptide comprising amino acids 2 to 476 of SEQ ID NO:2, wherein said amino acids 2 to 476 comprise a polypeptide of SEQ ID NO:2 minus the start methionine;
- j.) a RET16 variant protein encoded by a nucleic acid sequence encoding the protein having an amino acid sequence of SEQ ID NO:13;

- k.) an isolated RET16.2 variant protein encoded by the nucleic acid sequence of ATCC Deposit Accession No. PTA-3161;
- l.) a RET16 variant protein encoded by the polynucleotide sequence of SEQ ID NO:12;
- m.) an isolated polypeptide comprising amino acids 2 to 384 of SEQ ID NO:13, wherein said amino acids 2 to 384 comprise a polypeptide of SEQ ID NO:13 minus the start methionine;
- n.) a RET16 variant protein encoded by a nucleic acid sequence encoding the protein having an amino acid sequence of SEQ ID NO:15;
- o.) an isolated RET16.3 variant protein encoded by the nucleic acid sequence of ATCC Deposit Accession No. PTA-3161;
- p.) a RET16 variant protein encoded by the polynucleotide sequence of SEQ ID NO:14;
- q.) an isolated polypeptide comprising amino acids 2 to 502 of SEQ ID NO:15, wherein said amino acids 2 to 502 comprise a polypeptide of SEQ ID NO:15 minus the start methionine;
- r.) a RET16 protein encoded by a nucleic acid sequence encoding the protein having an amino acid sequence of SEQ ID NO:7;
- s.) a RET16 protein encoded by the polynucleotide sequence of SEQ ID NO:6;
- t.) an isolated polypeptide comprising amino acids 2 to 475 of SEQ ID NO:7, wherein said amino acids 2 to 475 comprise a polypeptide of SEQ ID NO:7 minus the start methionine;
- u.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 82% sequence identity to the sequence set forth in SEQ ID NO:13; and
- v.) a substantially purified cell signaling protein involved in the cell signaling cascade comprising an amino acid sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO:15.

6. A purified antibody which binds specifically to the protein or polypeptide according to claim 5, or an antigenic epitope thereof.

7. A method for producing a protein involved in the cell signaling cascade comprising the steps of:

- a) culturing the host cell according to claim 4 under conditions suitable for the expression of the polypeptide; and
- b) recovering the polypeptide from the host cell culture.

8. A method of detecting a polynucleotide encoding a cell signaling cascade protein, or fragment thereof, in a biological sample, comprising the steps of:

- a) hybridizing the polynucleotide according to claim 1 to the nucleic acid material of the biological sample, thereby forming a hybridization complex; and
- b) detecting the hybridization complex, wherein the presence of the complex correlates with the presence of a polynucleotide encoding ubiquitin conjugating enzyme, or a fragment thereof, in the biological sample.

9. A method of screening a library of molecules or compounds with a polynucleotide encoding a protein involved in the cell signaling cascade to identify at least one molecule or compound therein which specifically binds to the polynucleotide sequence, comprising:

- a) combining the polynucleotide according to claim 1 with a library of test molecules or compounds under conditions to allow specific binding; and
- b) detecting specific binding, thereby identifying a test molecule or compound which specifically binds to the polynucleotide sequence.

10. A method of screening for candidate compounds capable of modulating activity of a cell signaling protein involved in the cell signaling cascade, comprising:

- a) contacting a test compound with a cell or tissue expressing the protein according claim 5; and
- b) selecting as candidate modulating compounds those test compounds that modulate activity of the protein involved in the cell signaling cascade.

11. A method of treating an inflammation-related disease or disorder in a

mammal comprising administration of the protein according to claim 5 in an amount effective to treat the inflammation-related disease or disorder.

12. The method according to claim 11, wherein the disease or disorder is selected from the group consisting of rheumatoid arthritis, juvenile arthritis, psoriasis, asthma, ischemia-reperfusion, multiple sclerosis, rejection of organ or tissue transplants, chronic obstructive pulmonary disease; inflammatory bowel disease, Crohn's disease, ulcerative colitis, inacute respiratory distress syndrome, systemic lupus erythematosus, cystic fibrosis, autoimmune diseases, cancers, tumors and neoplasms.

13. A method of screening for compounds which inhibit or prevent binding of a human cell signaling protein with a second cell signaling protein, comprising:

- (a) contacting the cell signaling protein according claim 5 with a second cell signaling molecule with which it binds or associates in the presence or absence of a test compound under conditions which permit binding; and
- (b) determining if the level of binding of the cell signaling protein with the second cell signaling molecule is reduced or inhibited by comparing the level of binding in the presence of the test compound with that in the absence of the test compound.

14. A method of identifying compounds that inhibit the phosphorylation of a cell signaling cascade protein by protein kinases, comprising:

- (a) binding the cell signaling cascade protein according to claim 5 to a solid substrate in a reaction buffer containing  $^{32}\text{P}$ -gamma-ATP under conditions to allow binding of the cell signaling protein to the substrate;
- (b) adding protein kinase in the presence or absence of a test compound; and
- (c) determining of the presence of the test compound results in a decrease in the amount of  $^{32}\text{P}$  label that is incorporated into the cell signaling cascade protein, compared with the level of phosphorylation observed in the absence of the test compound to identify a test compound that inhibits phosphorylation of the cell signaling cascade protein.

15. An isolated polynucleotide consisting of a polynucleotide sequence selected from the group consisting of:

- a.) an isolated polynucleotide encoding a human RET16 polypeptide;
- b.) an isolated polynucleotide consisting of nucleotides 151 to 1575 of SEQ ID NO:1, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 476 of SEQ ID NO:2 minus the start codon;
- c.) an isolated polynucleotide consisting of nucleotides 148 to 1575 of SEQ ID NO:1, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 476 of SEQ ID NO:2 including the start codon;
- d.) an isolated polynucleotide encoding a human RET16.2 polypeptide;
- e.) an isolated polynucleotide consisting of nucleotides 114 to 1262 of SEQ ID NO:12, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 384 of SEQ ID NO:13 minus the start codon;
- f.) an isolated polynucleotide consisting of nucleotides 111 to 1262 of SEQ ID NO:12, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 384 of SEQ ID NO:13 including the start codon;
- g.) an isolated polynucleotide having a nucleotide sequence at least 68.2% identical to SEQ ID NO:12
- h.) an isolated polynucleotide encoding a human RET16.3 polypeptide;
- i.) an isolated polynucleotide consisting of nucleotides 139 to 1641 of SEQ ID NO:14, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 502 of SEQ ID NO:15 minus the start codon;
- j.) an isolated polynucleotide consisting of nucleotides 136 to 1641 of SEQ ID NO:14, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 502 of SEQ ID NO:15 including the start codon;

- k.) an isolated polynucleotide consisting of a polynucleotide having a nucleotide sequence at least 93.1% identical to SEQ ID NO:14
- l.) an isolated polynucleotide encoding a mouse RET16 polypeptide;
- m.) an isolated polynucleotide consisting of nucleotides 22 to 1443 of SEQ ID NO:6, wherein said nucleotides encode a polypeptide corresponding to amino acids 2 to 475 of SEQ ID NO:4 minus the start codon;
- n.) an isolated polynucleotide consisting of nucleotides 19 to 1443 of SEQ ID NO:6, wherein said nucleotides encode a polypeptide corresponding to amino acids 1 to 475 of SEQ ID NO:7 including the start codon;
- o.) a polynucleotide which is fully complementary to the polynucleotide according to any one of (a) through (n),
- p.) an isolated polynucleotide wherein the complementary nucleic acid sequence hybridizes to either strand of a denatured, double-stranded polynucleotide comprising the nucleic acid sequence selected from any one of (a) through (o) under conditions of moderate or high stringency;
- q.) the polynucleotide according to (p), wherein the conditions of moderate stringency comprise washing in 0.2x SSPE or SSC and 0.2% SDS at a temperature of about 42°C to about 50°C;
- r.) the polynucleotide according to (p), wherein the conditions of high stringency permit hybridization of those nucleic acid sequences that form stable hybrids in 0.018 M NaCl at about 65°C;
- s.) an isolated and purified polynucleotide, or fragment thereof, encoding an amino acid sequence of a cell signaling polypeptide involved in the cell signaling cascade, said polypeptide having at least 82% sequence identity with the sequence of SEQ ID NO:13;
- t.) an isolated and purified polynucleotide, or fragment thereof, encoding an amino acid sequence of a cell signaling polypeptide involved in the cell signaling cascade, said polypeptide having at least 95%

sequence identity with the sequence of SEQ ID NO:15.

- u.) an isolated and purified polynucleotide, or fragment thereof, having at least 68.2% sequence identity with the sequence of SEQ ID NO:12; and
- v.) an isolated and purified polynucleotide, or fragment thereof, having at least 93.1% sequence identity with the sequence of SEQ ID NO:14.

16. A recombinant vector comprising the isolated nucleic acid molecule according to claim 15.

17. A recombinant host cell comprising the recombinant vector according to claim 16.

18. A substantially purified cell signaling protein consisting of a polypeptide sequence selected from the group consisting of:

- a) an isolated polypeptide consisting of amino acids 2 to 476 of SEQ ID NO:2, wherein said amino acids 2 to 476 comprise a polypeptide of SEQ ID NO:2 minus the start methionine;
- b) a RET16 variant protein encoded by a nucleic acid sequence encoding the protein having an amino acid sequence of SEQ ID NO:13;
- c) an isolated RET16.2 variant protein encoded by the nucleic acid sequence of ATCC Deposit Accession No. PTA-3161;
- d) a RET16 variant protein encoded by the polynucleotide sequence of SEQ ID NO:12;
- e) an isolated polypeptide consisting of amino acids 2 to 384 of SEQ ID NO:13, wherein said amino acids 2 to 384 comprise a polypeptide of SEQ ID NO:13 minus the start methionine;
- f) a RET16 variant protein encoded by a nucleic acid sequence encoding the protein having an amino acid sequence of SEQ ID NO:15;
- g) an isolated RET16.3 variant protein encoded by the nucleic acid sequence of ATCC Deposit Accession No. PTA-3161;

- h) a RET16 variant protein encoded by the polynucleotide sequence of SEQ ID NO:14;
- i) an isolated polypeptide consisting of amino acids 2 to 502 of SEQ ID NO:15, wherein said amino acids 2 to 502 comprise a polypeptide of SEQ ID NO:15 minus the start methionine;
- j) a RET16 protein encoded by a nucleic acid sequence encoding the protein having an amino acid sequence of SEQ ID NO:7;
- k) a RET16 protein encoded by the polynucleotide sequence of SEQ ID NO:6;
- l) an isolated polypeptide consisting of amino acids 2 to 475 of SEQ ID NO:7, wherein said amino acids 2 to 475 comprise a polypeptide of SEQ ID NO:7 minus the start methionine;
- m) a substantially purified cell signaling protein involved in the cell signaling cascade consisting of an amino acid sequence having at least 82% sequence identity to the sequence set forth in SEQ ID NO:13; and
- n) a substantially purified cell signaling protein involved in the cell signaling cascade consisting of an amino acid sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO:15.

19. The method according to claim 11, wherein the disease or disorder is selected from the group consisting of: disorders associated with aberrant activation of the TNF- $\alpha$  pathway, disorders associated with aberrant cellular migration, disorders associated with aberrant cellular proliferation, disorders associated with aberrant cellular metastasis, asthma, juvenile idiopathic arthritis, hematogenous metastases of tumor cells, hyperinsulinaemia, diabetes type 2, atherosclerosis, cardiovascular disease, tumour progression, metastasis, colon cancer, Wegener's granulomatosis, stem cell transplantation complications, thalassemia, atherosclerosis, autoimmune disease atherosclerosis, ischemia-reperfusion injury, acute lung injury, rheumatoid arthritis, graft rejection, systemic lupus, coronary

artery calcification, ischaemic heart, and allergic inflammation.

20. An antisense RET16 oligonucleotide which is complementary to a RET16 polynucleotide sequence selected from SEQ ID NO:1, SEQ ID NO:12, or SEQ ID NO:14.